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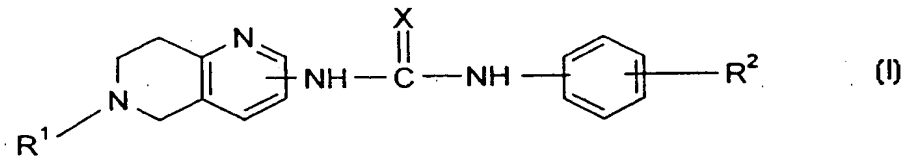

(I)

(57) Abstract

N–(naphthyridinyl)–N'–phenyl–ureas/thioureas of general formula (I) are useful for the treatment and/or prophylaxis of anxiety, mania, depression, panic disorders and/or aggression, disorders associated with a subarachnoid haemorrhage or neural shock, the effects associated with withdrawal from substances of abuse such as cocaine, nicotine, alcohol and benzodiazepines, disorders treatable and/or preventable with anti–convulsive agents, such as epilepsy including post–traumatic epilepsy, Parkinson's disease, psychosis, migraine, cerebral ischaemia, Alzheimer's disease and other degenerative diseases such as Huntingdon's chorea, schizophrenia, obsessive compulsive disorders (OCD), neurological deficits associated with AIDS, sleep disorders (including circadian rhythm disorders, insomnia and narcolepsy), tics (e.g. Giles de la Tourette's syndrome), traumatic brain injury, tinnitus, neuralgia, especially trigeminal neuralgia, neuropathic pain, dental pain, cancer pain, inappropriate neuronal activity resulting in neurodysthesias in diseases such as diabetes, multiple sclerosis (MS) and motor neurone disease, ataxias, muscular rigidity (spasticity), temporomandibular joint dysfunction, and amyotrophic lateral sclerosis (ALS).

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NOVEL COMPOUNDS

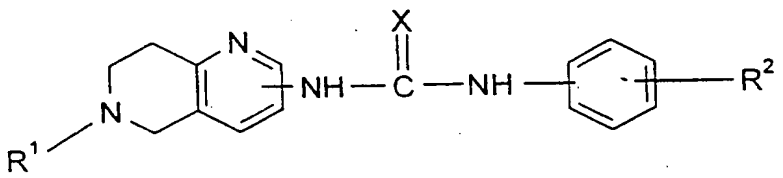
This invention relates to novel compounds, to processes for preparing them, and to their use as therapeutic agents.

EP-A- 0556008 (Shionogi) discloses condensed imidazopyridine derivatives with psychotropic activity, including the compound 1,6-naphthyridine-6(5H)-carboxylic acid, 4-azido-3-[[(1,1-dimethylethoxy) carbonyl] amino]-7,8-dihydro, ethyl ester.

WO96/39382 (Fujisawa) discloses the preparation of N-heterocycyl-ureas as 5-HT antagonists, including the compound N-(1-methyl-1H-indol-5-yl)-N'-(1,2,3,4-tetrahydro-7-isoquinolinyl)-urea.

It has now been surprisingly found that naphthyridinyl-urea compounds of formula (I) below possess anti-convulsant activity and are therefore believed to be useful in the treatment and/or prevention of anxiety, mania, depression, panic disorders and/or aggression, disorders associated with a subarachnoid haemorrhage or neural shock, the effects associated with withdrawal from substances of abuse such as cocaine, nicotine, alcohol and benzodiazepines, disorders treatable and/or preventable with anti-convulsive agents, such as epilepsy including post-traumatic epilepsy, Parkinson's disease, psychosis, migraine, cerebral ischaemia, Alzheimer's disease and other degenerative diseases such as Huntingdon's chorea, schizophrenia, obsessive compulsive disorders (OCD), neurological deficits associated with AIDS, sleep disorders (including circadian rhythm disorders, insomnia & narcolepsy), tics (e.g. Giles de la Tourette's syndrome), traumatic brain injury, tinnitus, neuralgia, especially trigeminal neuralgia, neuropathic pain, dental pain, cancer pain, inappropriate neuronal activity resulting in neurodysthesias in diseases such as diabetes, multiple sclerosis (MS) and motor neurone disease, ataxias, muscular rigidity (spasticity), temporomandibular joint dysfunction, and amyotrophic lateral sclerosis (ALS).

Accordingly, the present invention provides a compound of formula (I) or pharmaceutically acceptable salt thereof:



(I)

where X is O or S

R^1 is hydrogen, phenylC_{1-6} alkyl or C_{1-6} alkyl;

R^2 is hydrogen or up to three substituents independently selected from halogen, NO_2, CN, N_3, C_{1-6} alkylO-, C_{1-6} alkylS-, C_{1-6} alkyl, C_{1-6}haloalkyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkyl-C_{1-4}alkyl-, C_{1-6}alkenyl, C_{1-6}alkynyl, C_{1-6}haloalkylCO-, C_{1-6}alkylCO-, C_{3-6}cycloalkylCO-, C_{3-6}cycloalkyl-C_{1-4}alkylCO-, phenyl, phenoxy, benzyloxy, benzoyl, phenyl-C_{1-4}alkyl-, O-C_{1-6}haloalkyl, CO_2C_{1-4}alkyl, $S(O)_2C_{1-6}$alkyl, C_{1-4}alkylsulfamoyl or heterocyclyl, or $-NR^6R^7$ where

R^6 is hydrogen, C_{1-4} alkyl or $S(O)_2C_{1-6}$alkyl, and

R^7 is hydrogen, C_{1-4}alkyl, -CHO, $S(O)_2C_{1-6}$alkyl $-CO_2C_{1-4}$alkyl or $-COC_{1-4}$alkyl,

or an adjacent pair of R^2 groups together with the carbon atoms to which they are attached form an optionally substituted carbocyclic or heterocyclic ring.

The compounds of this invention are typically N-(tetrahydronaphthyridinyl), N'-optionally substituted phenyl-ureas or thioureas. Especially the compounds of the invention are (tetrahydronaphthyridin-3-yl) ureas or thioureas. The phenyl moiety may be substituted by up to three, preferably 2 or 1, groups.

In the formula (I), alkyl groups, including alkyl groups that are part of another moiety, may be straight chain or branched. Aromatic rings, such as the aromatic ring in the bicyclic heterocyclic moiety in formula (I) and phenyl groups, including phenyl groups that are part of other moieties, in R^2 may optionally be substituted with one or more independently selected substituents such as halogen or C_{1-6} alkyl, C_{1-6} alkoxy or C_{1-6} alkylcarbonyl groups, or other optional subtituents indicated below.

Suitable C_{3-6} cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

Suitable halo substituents include fluoro, chloro, iodo and bromo, which may also appear in haloalkyl, haloalkyloxy and haloalkyl carbonyl groups mentioned above, examples of which are trifluoromethyl, trifluoromethoxy and trifluoroacetyl.

When any R^2 represents heterocyclyl, this group is preferably a 5- to 10-membered monocyclic or bicyclic ring, which may be saturated or unsaturated, for example containing

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1, 2 or 3 heteroatoms selected from oxygen, nitrogen or sulphur, for example oxazolyl, thienyl or piperidinyl. The heterocyclyl group may contain up to 5, more preferably 1, 2 or 3 optional substituents.

Preferably a substituent for a heterocyclyl group is selected from halogen, (C_{1-6})alkyl, aryl(C_{1-6})alkyl, (C_{1-6})alkoxy, (C_{1-6})alkoxy(C_{1-6})alkyl, halo(C_{1-6})alkyl, hydroxy, amino, mono- and di-N-(C_{1-6})alkyl-amino, acylamino, carboxy, carboxy salts, carboxy esters, carbamoyl, mono- and di-N-(C_{1-6})alkylcarbonyl, aryloxycarbonyl, (C_{1-6})alkoxycarbonyl(C_{1-6})alkyl, aryl, oxy groups, ureido, guanidino, sulphonylamino, aminosulphonyl, (C_{1-6})alkylthio, (C_{1-6})alkylsulphinyl, (C_{1-6})alkylsulphonyl, heterocyclyl and heterocyclyl(C_{1-6})alkyl.

When an adjacent pair of R^2 together with the carbon atoms to which they are attached form a carbocyclic or heterocyclic ring, it is preferably a 5- to 7-membered ring, which may be aromatic or non-aromatic. Heterocyclic rings preferably contain 1, 2 or 3 heteroatoms selected from oxygen, nitrogen and sulphur; for example, pyrrole or pyrrolidine. A carbocyclic or heterocyclic ring formed by an adjacent pair of R^2 together with the carbon atoms to which they are attached may be optionally substituted on carbon or nitrogen by one or more substituents, e.g. up to 3 substituents. Examples of suitable substituents for the carbocyclic or heterocyclic ring include; halogen, (C_{1-6})alkyl, aryl(C_{1-6})alkyl, (C_{1-6})alkoxy, (C_{1-6})alkoxy(C_{1-6})alkyl, halo(C_{1-6})alkyl, hydroxy, amino, mono- and di-N-(C_{1-6})alkyl-amino, acylamino, carboxy, carboxy salts, carboxy esters, carbamoyl, mono- and di-N-(C_{1-6})alkylcarbonyl, aryloxycarbonyl, (C_{1-6})alkoxycarbonyl(C_{1-6})alkyl, aryl, oxy groups, ureido, guanidino, sulphonylamino, aminosulphonyl, (C_{1-6})alkylthio, (C_{1-6})alkylsulphinyl, (C_{1-6})alkylsulphonyl, heterocyclyl and heterocyclyl(C_{1-6})alkyl.

A suitable group of compounds of formula (I) have

R^1 as hydrogen, benzyl, methyl, ethyl, *iso*-propyl or *t*-butyl

R^2 as hydrogen, methyl, ethyl, *n*-butyl, *iso*-propyl, *t*-butyl, phenyl, benzyl, methoxy, ethoxy, *n*-propoxy, *iso*-propoxy, *n*-butoxy, phenoxy, benzyloxy, bromo, chloro, iodo, fluoro, nitro, cyano, acetyl, pivaloyl, *iso*-butyroyl, benzoyl, trifluoromethyl, trifluoromethoxy, trifluoroacetyl, carbomethoxy, carboethoxy, methylthio, *n*-propylsulfonyl, isopropylsulfonyl, dimethylsulfamoyl or oxazolyl,

or two R^2 groups linked to form naphthyl, indolyl or indolinyl, optionally substituted by acetyl or methyl.

In a particular group of compounds of formula (I),

R^1 is hydrogen or methyl,

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R^2 is hydrogen, methoxy, ethoxy, bromo, chloro, nitro, trifluoromethyl, or trifluoromethoxy.

Examples of compounds of formula (I) are:
N-(6-methyl-5,6,7,8-tetrahydro[1,6]naphthyridin-3-yl)-N'-(3-trifluoromethylphenyl)urea
N-(6-methyl-5,6,7,8-tetrahydro[1,6]naphthyridine-3-yl)-N'-(4-trifluoromethoxyphenyl)urea
N-(6-methyl-5,6,7,8-tetrahydro[1,6]naphthyridine-3-yl)-N'-(3-nitrophenyl)urea
N-(6-methyl-5,6,7,8-tetrahydro[1,6]naphthyridine-3-yl)-N'-(3-methoxyphenyl)urea
N-(6-methyl-5,6,7,8-tetrahdyro[1,6]naphthyridine-3-yl)-N'-(3-bromophenyl)urea
N-(6-methyl-5,6,7,8-tetrahdyro[1,6]naphthyridine-3-yl)-N'-(4-trifluoromethylphenyl)urea
N-(6-methyl-5,6,7,8-tetrahydro[1,6]naphthyridine-3-yl)-N'-(phenyl)urea
N-(6-methyl-5,6,7,8-tetrahydro[1,6]naphthyridine-3-yl)-N'-(5-chloro-2,4-dimethoxyphenyl)urea
N-(6-methyl-5,6,7,8-tetrahydro[1,6]naphthyridine-3-yl)-N'-(4-ethoxyphenyl)urea.

When synthesised, these compounds may be obtained in salt form, such as the hydrochloride or trifluoroacetate, and such salts also form part of this invention. Such salts may be used in preparing pharmaceutically acceptable salts. The compounds and their salts may be obtained as solvates, such as hydrates, and these also form part of this invention.

The above-listed compounds and pharmaceutically acceptable salts thereof, especially the hydrochloride, and pharmaceutically acceptable solvates, especially hydrates, form a preferred aspect of the present invention.

Where compounds of the present invention possess chiral centres and as such may exist in different enantiomeric forms, the present invention extends to each enantiomeric form and mixtures thereof including diastereoisomers and racemates.

The compounds of this invention possess anti-convulsant activity and are therefore believed to be useful for adminstration to mammals in the treatment and/or prevention of the disorders mentioned above, especially for humans, but also as a veterinary treatment. The administration of such compounds to a mammal may be by way of oral, parenteral, sub-lingual, nasal, rectal, topical or transdermal administration.

An amount effective to treat the disorders hereinbefore described depends on the usual factors such as the nature and severity of the disorders being treated and the weight of the mammal. However, a unit dose will normally contain 1 to 1000 mg, suitably 1 to 500 mg, for example an amount in the range of from 2 to 400 mg such as 2, 5, 10, 20, 30, 40, 50,

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100, 200, 300 and 400 mg of the active compound. Unit doses will normally be administered once or more than once per day, for example 1, 2, 3, 4, 5 or 6 times a day, more usually 1 to 4 times a day, such that the total daily dose is normally in the range, for a 70 kg adult of 1 to 1000 mg, for example 1 to 500 mg, that is in the range of approximately 0.01 to 15 mg/kg/day, more usually 0.1 to 6 mg/kg/day, for example 1 to 6 mg/kg/day.

It is greatly preferred that the compound of formula (I) is administered in the form of a unit-dose composition, such as a unit dose oral, including sub-lingual, nasal, rectal, topical or parenteral (especially intravenous) composition.

Such compositions are prepared by admixture and are suitably adapted for oral or parenteral administration, and as such may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, injectable and infusable solutions or suspensions or suppositories. Orally administrable compositions are preferred, in particular shaped oral compositions, since they are more convenient for general use.

Tablets and capsules for oral administration are usually presented in a unit dose, and contain conventional excipients such as binding agents, fillers, diluents, tabletting agents, lubricants, disintegrants, colourants, flavourings, and wetting agents. The tablets may be coated according to well known methods in the art.

Suitable fillers for use include cellulose, mannitol, lactose and other similar agents. Suitable disintegrants include starch, polyvinylpyrrolidone and starch derivatives such as sodium starch glycollate. Suitable lubricants include, for example, magnesium stearate. Suitable pharmaceutically acceptable wetting agents include sodium lauryl sulphate.

These solid oral compositions may be prepared by conventional methods of blending, filling, tabletting or the like. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers. Such operations are, of course, conventional in the art.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups, or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, gelatin, hydroxyethylcellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats, emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example,

almond oil, fractionated coconut oil, oily esters such as esters of glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl *p*-hydroxybenzoate or sorbic acid, and if desired conventional flavouring or colouring agents.

Oral formulations also include conventional sustained release formulations, such as tablets or granules having an enteric coating.

For parenteral administration, fluid unit dose forms are prepared containing the compound and a sterile vehicle. The compound, depending on the vehicle and the concentration, can be either suspended or dissolved. Parenteral solutions are normally prepared by dissolving the compound in a vehicle and filter sterilising before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are also dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum.

Parenteral suspensions are prepared in substantially the same manner except that the compound is suspended in the vehicle instead of being dissolved and sterilised by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound of the invention.

As is common practice, the compositions will usually be accompanied by written or printed directions for use in the medical treatment concerned.

Accordingly, in a further aspect, the present invention provides a pharmaceutical composition for use in the treatment and/or prophylaxis of anxiety, mania, depression, panic disorders and/or aggression, disorders associated with a subarachnoid haemorrhage or neural shock, the effects associated with withdrawal from substances of abuse such as cocaine, nicotine, alcohol and benzodiazepines, disorders treatable and/or preventable with anti-convulsive agents, such as epilepsy including post-traumatic epilepsy, Parkinson's disease, psychosis, migraine, cerebral ischaemia, Alzheimer's disease and other degenerative diseases such as Huntingdon's chorea, schizophrenia, obsessive compulsive disorders (OCD), neurological deficits associated with AIDS, sleep disorders (including circadian rhythm disorders, insomnia & narcolepsy), tics (e.g. Giles de la Tourette's syndrome), traumatic brain injury, tinnitus, neuralgia, especially trigeminal neuralgia, neuropathic pain, dental pain, cancer pain, inappropriate neuronal activity resulting in neurodysthesias in diseases such as diabetes, multiple sclerosis (MS) and motor neurone disease, ataxias, muscular rigidity (spasticity), temporomandibular joint dysfunction, and amyotrophic lateral sclerosis (ALS), which comprises a compound of formula (I), or a

pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier.

The present invention also provides a method of treatment and/or prophylaxis of anxiety, mania, depression, panic disorders and/or aggression, disorders associated with a subarachnoid haemorrhage or neural shock, the effects associated with withdrawal from substances of abuse such as cocaine, nicotine, alcohol and benzodiazepines, disorders treatable and/or preventable with anti-convulsive agents, such as epilepsy including post-traumatic epilepsy, Parkinson's disease, psychosis, migraine, cerebral ischaemia, Alzheimer's disease and other degenerative diseases such as Huntingdon's chorea, schizophrenia, obsessive compulsive disorders (OCD), neurological deficits associated with AIDS, sleep disorders (including circadian rhythm disorders, insomnia & narcolepsy), tics (e.g. Giles de la Tourette's syndrome), traumatic brain injury, tinnitus, neuralgia, especially trigeminal neuralgia, neuropathic pain, dental pain, cancer pain, inappropriate neuronal activity resulting in neurodysthesias in diseases such as diabetes, multiple sclerosis (MS) and motor neurone disease, ataxias, muscular rigidity (spasticity), temporomandibular joint dysfunction, and amyotrophic lateral sclerosis (ALS), comprising administering to the sufferer in need thereof an effective or prophylactic amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof.

In a further aspect the invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, for the manufacture of a medicament for the treatment and/or prophylaxis of anxiety, mania, depression, panic disorders and/or aggression, disorders associated with a subarachnoid haemorrhage or neural shock, the effects associated with withdrawal from substances of abuse such as cocaine, nicotine, alcohol and benzodiazepines, disorders treatable and/or preventable with anti-convulsive agents, such as epilepsy including post-traumatic epilepsy, Parkinson's disease, psychosis, migraine, cerebral ischaemia, Alzheimer's disease and other degenerative diseases such as Huntingdon's chorea, schizophrenia, obsessive compulsive disorders (OCD), neurological deficits associated with AIDS, sleep disorders (including circadian rhythm disorders, insomnia & narcolepsy), tics (e.g. Giles de la Tourette's syndrome), traumatic brain injury, tinnitus, neuralgia, especially trigeminal neuralgia, neuropathic pain, dental pain, cancer pain, inappropriate neuronal activity resulting in neurodysthesias in diseases such as diabetes, multiple sclerosis (MS) and motor neurone disease, ataxias, muscular rigidity (spasticity), temporomandibular joint dysfunction, and amyotrophic lateral sclerosis (ALS).

In a further aspect the invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate, thereof as a therapeutic agent, in particular for the treatment and/or prophylaxis of anxiety, mania, depression, panic disorders and/or

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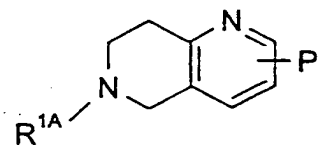
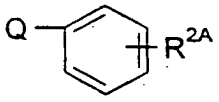
aggression, disorders associated with a subarachnoid haemorrhage or neural shock, the effects associated with withdrawal from substances of abuse such as cocaine, nicotine, alcohol and benzodiazepines, disorders treatable and/or preventable with anti-convulsive agents, such as epilepsy including post-traumatic epilepsy, Parkinson's disease, psychosis, migraine, cerebral ischaemia, Alzheimer's disease and other degenerative diseases such as Huntingdon's chorea, schizophrenia, obsessive compulsive disorders (OCD), neurological deficits associated with AIDS, sleep disorders (including circadian rhythm disorders, insomnia & narcolepsy), tics (e.g. Giles de la Tourette's syndrome), traumatic brain injury, tinnitus, neuralgia, especially trigeminal neuralgia, neuropathic pain, dental pain, cancer pain, inappropriate neuronal activity resulting in neurodysthesias in diseases such as diabetes, multiple sclerosis (MS) and motor neurone disease, ataxias, muscular rigidity (spasticity), temporomandibular joint dysfunction, and amyotrophic lateral sclerosis (ALS).

Another aspect of the invention provides a process for the preparation of compounds of formula (I), which comprises reacting a compound of formula (II)



(II)

where R^{1A} is R^1 as defined for formula (I) or a group convertible to R^1, and
P is NH_2 or NCX, X being as defined for formula (I),
with a compound of formula (III)



(III)

where Q is NCX or NH_2 and different from P, X being as defined for formula (I), and
R^{2A} is R^2 as defined for formula (I) or a group or groups convertible to R^2,
and where required converting a R^{1A} or R^{2A} group to a R^1 or R^2 group, converting one R^1 or R^2 group to another R^1 or R^2 group, converting a salt product to the free base or another pharmaceutically acceptable salt, or converting a free base product to a pharmaceutically acceptable salt.

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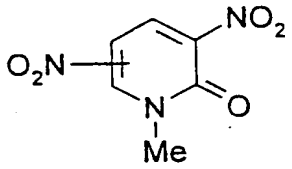
Conventional conditions for condensation of isocyanates or isothiocyanates with amines may be used, for example treatment in an inert solvent such as toluene, DMF or dichloromethane at ambient or elevated temperature.

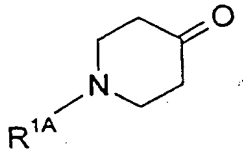
Conversions of an R^{1A} or R^{2A} group to a R^1 or R^2 group typically arise when a protecting group is needed during the above coupling reaction or during the preparation of the reactants by the procedures described below. Interconversion of one R^1 or R^2 group to another typically arises when one compound of formula (I) is used as the immediate precursor of another compound of formula (I), or when it is easier to introduce a more complex or reactive substituent at the end of a synthetic sequence.

Compounds of formula (II) in which P is NH_2 may be prepared starting from a compound of formula (IV), such as a dinitro-1-methyl-2-pyridone



(IV)

by reaction with a compound of formula (V)



V)

in a solution of ammonia in a suitable solvent such as methanol, to obtain a compound of formula (VI) using a procedure similar to that of s Takada et al, J Med Chem, 1996, **39**, 2844.

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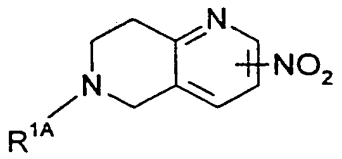

(VI)

Compounds of formula (VI) may be converted to compounds of formula (II) by hydrogenation or reduction of the nitro group. For example, a compound of formula (VI) may be hydrogenated by treatment with hydrogen in a suitable solvent such as methanol in the presence of a palladium/carbon catalyst. Alternatively, a compound of formula (VI) may be reduced with stannous chloride in concentrated hydrochloric acid in a suitable solvent such as ethanol.

Compounds of formula (IV) may be prepared using the procedure of E. Matsumura, M. Ariga and Y. Tohda, Bull. Chem. Soc. Japan, 52 (8), 2413-2419 (1979).

Compounds of formula (III) in which Q is iso(thio)cyanate are commercially available or may be prepared by formation of iso(thio)cyanates from commercially available substituted phenyl compounds using conventional procedures such as described by I T Forbes *et al* , J.Med.Chem., 1993, 36, 1104, and in Fieser and Fieser, Reagents for Organic Synthesis Vol I. For example an isocyanate may be prepared by stirring a relevant amine with one equivalent of carboxyl diimidazole in a suitable solvent such as dichloromethane at room temperature, and then evaporated to dryness *in vacuo*. Isothiocyanates may be prepared by reaction of the relevant amine with carbon disulphide in pyridine in the presence of dicyclohexylcarbodiimide.

Compounds of formula (II) in which P is iso(thio)cyanate may be similarly prepared starting from the amines of formula (II) described above.

Compounds of formula (III) in which Q is NH_2 are commercially available or may be prepared by formation of amines on commercially available substituted phenyl compounds using conventional procedures.

Where intermediates disclosed for the above processes are novel compounds, they also form part of this invention.

The compounds of the present invention may contain a chiral centre, and therefore the above processes may produce a mixture of diastereoisomers. A single diastereoisomer may

be prepared by separating such a mixture of diastereoisomers which has been synthesised using a racemic starting material, or by synthesis using an optically pure starting material.

The compounds of this invention may be in crystalline or non-crystalline form, and, if crystalline, may optionally be hydrated or solvated. When some of the compounds of this invention are allowed to crystallise or are recrystallised from organic solvents, solvent of crystallisation may be present in the crystalline product. Similarly, some of the compounds of this invention may be crystallised or recrystallised from solvents containing water. In such cases water of hydration may be present in the crystalline product. Crystallisation procedures will usually produce stoichiometric hydrates. Compounds containing variable amounts of water may be produced by processes such as lyophilisation.

The compounds according to the invention are suitably provided in substantially pure form, for example at least 50% pure, suitable at least 60% pure, advantageously at least 75% pure, preferably at least 85% pure, more preferably at least 95% pure, especially at least 98% pure, all percentages being calculated as weight/weight. An impure or less pure form of a compound according to the invention may, for example, be used in the preparation of a more pure form of the same compound or of a related compound (for example a corresponding derivative) suitable for pharmaceutical use.

The present invention also includes pharmaceutically acceptable salts and derivatives of the compounds of the invention. Salt formation may be possible when one of the substituents carries an acidic or basic group. Salts may be prepared by salt exchange in conventional manner.

Acid-addition salts may be pharmaceutically acceptable or non-pharmaceutically acceptable. In the latter case, such salts may be useful for isolation and purification of the compound of the invention, or intermediates thereto, and will subsequently be converted into a pharmaceutically acceptable salt or the free base.

The preparation of compounds of formula (II) is illustrated by the following Descriptions; the preparation of compounds of this invention is illustrated by the following Examples. The utility of compounds of this invention is shown by the Pharmacological Data that follow the Examples.

Description 1

6-Benzyl-3-nitro-5,6,7,8-tetrahydro[1,6]naphthyridine

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3,5-Dinitro-1-methyl-2-pyridone[1] (1.99g; 10 mmol) was added to a solution of ammonia in methanol (1.1M; 100ml; 110 mmol) and the resulting solution treated with 1-benzyl-4-piperidone (2.27g; 12 mmol). The resulting mixture was heated at 60°c for 5h, cooled to room temperature and evaporated to dryness under reduced pressure. The residue was purified by chromatography through SiO_2 eluting with 50% ethyl acetate/60-80° petrolium ether to give the title compound (2.5g; 93%). Recrystallisation from ethyl acetate - 60 - 80° petroleum ether gave the title compound as a pale yellow, microcrystalline solid, mp 108°C;

(250MHz; $CDCl_3$) δ_H: 3.03 (2H, t, J = 6 Hz), 3.28 (2H, t, J = 6 Hz), 3.83 and 3.87 (each 2H, 2s), 7.38 - 7.49 (5H, m), 8.21 (1H, d, J = 2Hz), 9.33 (1H, d, J = 2 Hz)

1. E. Matsumura, M. Ariga and Y. Tohda, Bull. Chem. Soc. Japan, 52 (8), 2413-2419 (1979).

Description 2

3-Amino-6-benzyl-5,6,7,8-tetrahydro[1,6]naphthyridine

6-Benzyl-3-nitro-5,6,7,8-tetrahydro[1,6]naphthyridine (790mg; 2.93 mmol) was dissolved in ethanol (100ml), the solution heated at 50°C and treated with a solution of stannous chloride dihydrate (2.65g; 11.73 mmol) in conc. hydrochloric acid (10ml). After 10 min, the reaction mixture was concentrated under reduced pressure, neutralised by addition of 2M aqueous sodium hydroxide and extracted with DCM. The extracts were combined, washed with water, saturated brine, dried ($MgSO_4$) and evaporated to dryness *in vacuo*. The brown residue was dissolved in methanol and SiO_2 added. The volatiles were removed under reduced pressure and the dried SiO_2 placed on the top of a silica column and subjected to chromatography, eluting with ethanol in ethyl acetate (0->20%) ethanol gradient. The title compound was obtained as a white powder (275mg; 39%).

(250MH, $(CD_3)_2SO$) δ_H: 2.33 (4H, br m), 3.25 (2H, s), 3.45 (2H, br s), 4.84 (2H, br s, exchangeable), 6.37 (1H, br s), 7.11 - 7.22 (5H, m), 7.56 (1H, br s)

Description 3

6-Methyl-3-nitro-5,6,7,8-tetrahydro[1,6]naphthyridine

3,5-Dinitro-1-methyl-2-pyridone (5.97g; 30 mmol) was treated with 1.22M ammonia in methanol (300ml) followed by 1-methyl-4-piperidone (3.73g, 33 mmol) and the mixture

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heated at 60° for 5h, then allowed to stand at ambient temp for 72h. Evaporated to dryness under reduced pressure and the orange/red residue triturated under a mixture of dichloromethane and diethyl ether, collected by filtration, washed with diethyl ether and dried in air. Chromatography through silica gel, eluting with ethyl acetate, gave the title compound as a red solid (3.4g, 59%); ν_{max} (CH_2Cl_2) 1530 and 1351cm^{-1}

(250MHz; $CDCl_3$) :δ_H: 2.53 (3H, s), 2.85 (2H, t, J = 6 Hz), 3.18 (2H, t, J = 6 Hz), 3.69 (2H, s), 8.14 (1H, d, J = 2 Hz), 9.23 (1H, d, J = 2 Hz)

Description 4

3-Amino-6-methyl-5,6,7,8-tetrahydro[1,6]naphthyridine

6-Methyl-3-nitro-5,6,7,8-tetrahydro[1,6]naphthyridine (2.72g, 1.41 mmol) was dissolved in methanol (100ml) and treated with 10% palladium on carbon (1.0g). The mixture was hydrogenated for 2h. The catalyst was removed by filtration through Celite, the filter bed washed with methanol and the filtrate evaporated to dryness under reduced pressure to give a yellow solid, which was triturated under diethyl ether and the solids collected by filtration, washed with diethyl ether and dried *in vacuo* (1.89g, 83%)

(250MHz, $CDCl_3$) δ_H: 2.46 (3H, s), 2.75 (2H, t, J = 6 Hz), 2.95 (2H, t, J = 6 Hz), 3.50 (2H, s), 3.56 (2H, br s, exchangeable), 6.65 (1H, d, J = 2 Hz), 7.92 (1H, d, J = 2 Hz)

Example 1

N-(6-Methyl-5,6,7,8-tetrahydro[1,6]naphthyridin-3-yl)-N'-(3-trifluoromethylphenyl)urea, hydrochloride

3-Amino-6-methyl-5,6,7,8-tetrahydro-[1,6]-naphthyridine (163mg; 1 mmol) was dissolved in THF (20ml) and the solution treated with α,α,α-trifluoro-m-tolylisocyanate (187mg; 1 mmol). The resulting mixture was stirred at ambient temperature for 18h then evaporated to dryness under reduced pressure. The residual, brown solid was redissolved in THF (minimum volume) and the resulting solution treated with a solution of hydrogen chloride in diethyl ether (1.0M; 1ml; 1 mmol). This mixture was stirred at ambient temperature for 15 min. and the title compound collected by filtration, washed with THF and diethyl ether and dried under reduced pressure (366mg; 95%).

[250MHz; $(CD_3)_2SO$] δ_H: 2.84 (3H, br s); 2.90 - 3.30 (2H, m), 3.58 - 3.76 (2H, m), 4.20 - 4.40 (1H, m), 4.42 - 4.60 (1H, m), 7.21 - 7.27 (1H, m), 7.54 - 7.64 (2H, m), 7.78 - 7.81

(2H, m), 8.32 (1H, s, exchangeable), 8.46 (1H, d, J = 2 Hz), 9.90 (1H, s, exchangeable), 10.80 - 11.10 (1H, br s, exchangeable); $^{m}/_{z}$ (API^{+}): 351.1 $[M+H]^{+}$

Example 2

N-(6-Methyl-5,6,7,8-tetrahydro[1,6]naphthyridine-3-yl)-N'-(4-trifluoromethoxyphenyl)urea

The title compound was prepared in 82% yield from amine of Description 4 and 4-trifluoromethoxyphenyl isocyanate using a method similar to that of Example 1.

^{1}H NMR (250MHz, d^{6}-DMSO) δ: 2.21 (3H, s), 2.53 (2H, t, J = 6 Hz), 2.68 (2H, t, J = 6 Hz), 3.34 (2H, s), 7.14 (2H, d, J = 9 Hz), 7.41 (2H, d, J = 9 Hz), 7.48 (1H, d, J = 2 Hz), 8.20 (1H, d, J = 2 Hz), 8.65 (1H, s), 8.84 (1H, s); $^{m}/_{z}$ (API^{+}): 367 (MH^{+}; 33%).

Example 3

N-(6-Methyl-5,6,7,8-tetrahydro[1,6]naphthyridine-3-yl)-N'-(3-nitrophenyl)urea

The title compound was prepared in 75% yield from amine of Description 4 and 3-nitrophenyl isocyanate using a method similar to that of Example 1.

^{1}H NMR (250MHz, d^{6}-DMSO) δ: 2.23 (3H, s), 2.55 (2H, t, J = 6 Hz), 2.70 (2H, t, J = 6 Hz), 3.37 (2H, s), 7.44 (1H, t, J = 8 Hz), 7.53 (1H, d, J = 2 Hz), 7.60 (1H, dd, J = 2 and 8 Hz), 7.70 (1H, dd, J = 2 and 8 Hz), 8.24 (1H, d, J = 2 Hz), 8.43 (1H, t, J =2 Hz), 8.79 (1H, s), 9.20 (1H, s); $^{m}/_{z}$ (API^{+}): 328 (MH^{+}; 72%).

Example 4

N-(6-Methyl-5,6,7,8-tetrahydro[1,6]naphthyridine-3-yl)-N'-(3-methoxyphenyl)urea

The title compound was prepared in 20% yield from amine of Description 4 and 3-methoxyphenyl isocyanate using a method similar to that of Example 1.

^{1}H NMR (250MHz, d^{6}-DMSO) δ: 2.68 (3H, s), 2.84 (2H, t, J = 6 Hz), 3.00 (2H, t, J = 6 Hz), 3.66 (2H, s), 3.90 (3H, s), 6.74 (1H, d, J = 8 Hz), 7.10 (1H, d, J = 8 Hz), 7.35 (2H, m), 7.82 (1H, s), 8.50 (1H, s), 8.90 (1H, s), 8.96 (1H, s); $^{m}/_{z}$ (API^{+}): 313 (MH^{+}; 100%).

Example 5

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N-(6-Methyl-5,6,7,8-tetrahdyro[1,6]naphthyridine-3-yl)-N'-(3-bromophenyl)urea

The title compound was prepared in 86% yield from amine of Description 4 and 3-bromophenyl isocyanate using a method similar to that of Example 1.

^{1}H NMR (250MHz, d^6-DMSO) δ: 2.47 (3H, s), 2.79 (2H, t, J = 6 Hz), 2.95 (2H, t, J = 6 Hz), 3.61 (2H, s), 7.24 - 7.48 (3H, bm), 7.76 (1H, d, J = 2 Hz), 7.98 (1H, t, J = 2 Hz), 8.47 (1H, d, J = 2 Hz), 8.95 (1H, s), 9.10 (1H, s); $^m/_z$ (API$^+$): 361, 363 (MH$^+$; 43%)

Example 6

N-(6-methyl-5,6,7,8-tetrahdyro[1,6]naphthyridine-3-yl)-N'-(4-trifluoromethylphenyl)urea

The title compound was prepared in 65% yield from amine of Description 4 and 4-trifluoromethylphenyl isocyanate using a method similar to that of Example1.

^{1}H NMR (250MHz, d^6-DMSO) δ: 2.35 (3H, s), 2.67 (2H, t, J = 6 Hz), 2.83 (2H, t, J = 6 Hz), 3.49 (2H, s), 7.59 - 7.72 (5H, bm), 8.37 (1H, d, J = 2 Hz), 8.88 (1H, s), 9.21 (1H, s); $^m/_z$ (API$^+$): 351 (MH$^+$; 94%)

Example 7

N-(6-Methyl-5,6,7,8-tetrahydro[1,6]naphthyridine-3-yl)-N'-(phenyl)urea

The title compond was prepared in 74% yield from amine of Description 4 and phenyl isocyanate using a method similar to that of Example 1.

^{1}H NMR (250MHz, d^6-DMSO) δ: 2.30 (3H, s), 2.62 (2H, t, J = 6 Hz), 2.77 (2H, t, J = 6 Hz), 3.43 (2H, s), 6.92 (1H, t, J = 7 Hz), 7.23 (2H, dd, J = 7 and 8 Hz), 7.40 (2H, d, J = 8 Hz), 7.58 (1H, d, J = 2 Hz), 8.29 (1H, d, J = 2 Hz), 8.67 (1H, s), 8.70 (1H, s); $^m/_z$ (API$^+$): 283 (MH$^+$; 75%)

Example 8

N-(6-Methyl-5,6,7,8-tetrahydro[1,6]naphthyridine-3-yl)-N'-(5-chloro-2,4-dimethoxyphenyl)urea

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The title compound was prepared in 71% yield from amine of Description 4 and 5-chloro, 2,4-dimethoxyphenyl isocyanate using a method similar to that of Example 1.

^{1}H NMR (250MHz, d^6-DMSO) δ: 2.43 (3H, s), 2.75 (2H, t, J = 6 Hz), 2.90 (2H, t, J = 6 Hz), 3.57 (2H, s), 3.94 (3H, s), 4.01 (3H, s), 6.94 (1H, s), 7.72 (1H, d, J = 2 Hz), 8.20 (1H, s), 8.30 (1H, s), 8.38 (1H, d, J = 2 Hz), 9.37 (1H, s); $^m/_z$ (API$^+$): 377 (MH$^+$; 100%)

Example 9

N-(6-Methyl-5,6,7,8-tetrahydro[1,6]naphthyridine-3-yl)-N'-(4-ethoxyphenyl)urea

The title compound was prepared in 88% yield from amine D4 and 4-ethoxyphenyl isocyanate using a method similar to that of Example1.

^{1}H NMR (250MHz, d^6-DMSO) δ: 1.15 (3H, t, J = 7 Hz), 2.20 (3H, s), 2.51 (2H,t, J = 6 Hz), 2.67 (2H, t, J = 6 Hz), 3.33 (2H, s), 3.82 (2H, q, J = 7 Hz), 6.70 (2H, d, J = 9 Hz), 7.19 (2H, d, J = 9 Hz), 7.47 (1H, d, J = 2 Hz), 8.18 (1H, d, J = 2 Hz), .8.40 (1H, s), 8.50 (1H, s); $^m/_z$ (API$^+$): 327 (MH$^+$; 100%)

PHARMACOGICAL DATA

1. Binding Assay Method

WO 92/22293 (SmithKline Beecham) discloses compounds having anti-convulsant activity, including *inter alia* the compound *trans*-(+)-6-acetyl-4S-(4-fluorobenzoylamino)-3,4-dihydro-2,2-dimethyl-2H-1-benzopyran-3R-ol (hereinafter referred to as Compound A). It has been found that the compounds of WO 92/22293 bind to a novel receptor obtainable from rat forebrain tissue, as described in WO 96/18650 (SmithKline Beecham). The affinity of test compounds to the novel receptor site is assessed as follows.

Method

Whole forebrain tissue is obtained from rats. The tissue is first homogenised in buffer (usually 50mM Tris/HCl, pH 7.4). The homogenised tissue is washed by centrifugation and resuspension in the same buffer, then stored at -70°C until used.

To carry out the radioligand binding assay, aliquots of tissue prepared as above (usually at a concentration of 1-2mg protein/ml) are mixed with aliquots of [3H]-Compound A

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dissolved in buffer. The final concentration of [3H]-Compound A in the mixture is usually 20nM. The mixture is incubated at room temperature for 1 hour. [3H]-Compound A bound to the tissue is then separated from unbound [3H]-Compound A by filtration through Whatman GF/B glass fibre filters. The filters are then washed rapidly with ice-cold buffer. The amount of radioactivity bound to the tissue trapped on the filters is measured by addition of liquid scintillation cocktail to the filters followed by counting in a liquid scintillation counter.

In order to determine the amount of "specific" binding of [3H]-Compound A, parallel assays are carried out as above in which [3H]-Compound A and tissue are incubated together in the presence of unlabelled Compound A (usually 3 μM). The amount of binding of [3H]-Compound A remaining in the presence of this unlabelled compound is defined as "non-specific" binding. This amount is subtracted from the total amount of [3H]-Compound A binding (i.e. that present in the absence of unlabelled compound) to obtain the amount of "specific" binding of [3H]-Compound A to the novel site.

The affinity of the binding of test compounds to the novel site can be estimated by incubating together [3H]-Compound A and tissue in the presence of a range of concentrations of the compound to be tested. The decrease in the level of specific [3H]-Compound A binding as a result of competition by increasing concentrations of the compound under test is plotted graphically, and non-linear regression analysis of the resultant curve is used to provide an estimate of compound affinity in terms of pKi value.

Results

Compounds of this invention were active in this test with pKi values greater than 6. For example, compounds of Examples 3-8 gave pKi values greater than 7.5.

2. **MEST Test**

The maximal electroshock seizure (MEST) threshold test in rodents is particularly sensitive for detecting potential anticonvulsant properties[1]. In this model, anticonvulsant agents elevate the threshold to electrically-induced seizures whilst proconvulsants lower the seizure threshold.

Method

Mice (naive male, Charles River, U.K. CD-1 strain, 25 - 30g) are randomly assigned to groups of 10 - 20 and dosed orally or intraperitoneally at a dose volume of 10 ml/kg with

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various doses of compound (0.3 - 300 mg/kg) or vehicle. Mice are then subjected at 30 or 60 min post dose to a single electroshock (0.1 sec, 50Hz, sine wave form) administered via corneal electrodes. The mean current and standard error required to induce a tonic seizure in 50% (CC_{50}) of the mice in a particular treatment group is determined by the 'up and down' method of Dixon and Mood (1948)[2]. Statistical comparisons between vehicle- and drug-treated groups are made using the method of Litchfield and Wilcoxon (1949)[3].

In control animals the CC_{50} is usually 14 - 18 mA. Hence the first animal in the control group is subjected to a current of 16 mA. If a tonic seizure does not ensue, the current is increased for a subsequent mouse. If a tonic convulsion does occur, then the current is decreased, and so on until all the animals in the group have been tested.

The percentage increase or decrease in CC_{50} for each group compared to the control is calculated.

Studies are carried out using a Hugo Sachs Electronik Constant Current Shock Generator with totally variable control of shock level from 0 to 300 mA and steps of 2 mA are usually used.

Drugs are suspended in 1% methyl cellulose.

References

1. Loscher, W. and Schmidt, D. (1988). Epilepsy Res., 2, 145-181
2. Dixon, W.J. and Mood, A.M. (1948). J. Amer. Stat. Assn., 43, 109-126
3. Litchfield, J.T. and Wilcoxon, F.(1949). J. Pharmacol. exp. Ther., 96, 99-113

Results

Compounds of this invention dosed by the oral route as a suspension in methyl cellulose and tested one hour post dosing show an increase in seizure threshold. For example, at a dose of 10 mg/kg p.o. the compounds of Examples 3 and 7 showed statistically significant increases of 60% and 15% respectively.

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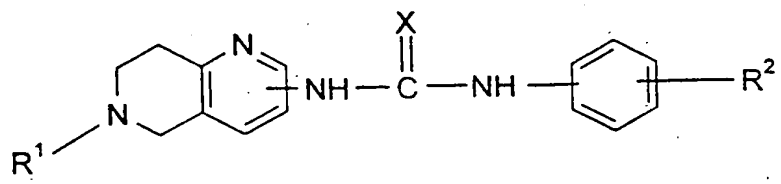
CLAIMS

1. A compound of formula (I) or pharmaceutically acceptable salt thereof:



(I)

where X is O or S

R^1 is hydrogen, phenylC_{1-6} alkyl or C_{1-6} alkyl,

R^2 is hydrogen or up to three substituents independently selected from halogen, NO_2, CN, N_3, C_{1-6} alkylO-, C_{1-6} alkylS-, C_{1-6} alkyl, C_{1-6}haloalkyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkyl-C_{1-4}alkyl-, C_{1-6}alkenyl, C_{1-6}alkynyl, C_{1-6}haloalkylCO-, C_{1-6}alkylCO-, C_{3-6}cycloalkylCO-, C_{3-6}cycloalkyl-C_{1-4}alkylCO-, phenyl, phenoxy, benzyloxy, benzoyl, phenyl-C_{1-4}alkyl-, O-C_{1-6}haloalkyl, CO_2C_{1-4}alkyl, $S(O)_2C_{1-6}$alkyl, C_{1-4}alkylsulfamoyl or heterocyclyl, or -NR^6R^7 where

R^6 is hydrogen, C_{1-4} alkyl or $S(O)_2C_{1-6}$alkyl, and

R^7 is hydrogen, C_{1-4}alkyl, -CHO, $S(O)_2C_{1-6}$alkyl -CO_2C_{1-4}alkyl or -COC_{1-4}alkyl,

or an adjacent pair of R^2 groups together with the carbon atoms to which they are attached form an optionally substituted carbocyclic or heterocyclic ring.

2. A compound of formula (I) which is a (tetrahydronaphthyridin-3-yl) urea or thiourea.

3. A compound of formula (I) in which

R^1 as hydrogen, benzyl, methyl, ethyl, *iso*-propyl or *t*-butyl

R^2 as hydrogen, methyl, ethyl, *n*-butyl, *iso*-propyl, *t*-butyl, phenyl, benzyl, methoxy, ethoxy, *n*-propoxy, *iso*-propoxy, *n*-butoxy, phenoxy, benzyloxy, bromo, chloro, iodo, fluoro, nitro, cyano, acetyl, pivaloyl, *iso*-butyroyl, benzoyl, trifluoromethyl, trifluoromethoxy, trifluoroacetyl, carbomethoxy, carboethoxy, methylthio, *n*-propylsulfonyl, isopropylsulfonyl, dimethylsulfamoyl or oxazolyl,

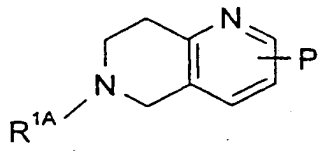
R^6 and R^7 are hydrogen, acetyl or methanesulfonyl,

or two R^2 groups linked to form naphthyl, indolyl or indolinyl, optionally substituted by acetyl or methyl.

4. A compound of formula (I) in which
R^1 is hydrogen or methyl,
R^2 is hydrogen or one or more of methoxy, ethoxy, bromo, chloro, nitro, trifluoromethyl or trifluoromethoxy.

5. A compound of formula (I) which is
N-(6-methyl-5,6,7,8-tetrahydro[1,6]naphthyridin-3-yl)-N'-(3-trifluoromethylphenyl)urea
N-(6-methyl-5,6,7,8-tetrahydro[1,6]naphthyridine-3-yl)-N'-(4-trifluoromethoxyphenyl)urea
N-(6-methyl-5,6,7,8-tetrahydro[1,6]naphthyridine-3-yl)-N'-(3-nitrophenyl)urea
N-(6-methyl-5,6,7,8-tetrahydro[1,6]naphthyridine-3-yl)-N'-(3-methoxyphenyl)urea
N-(6-methyl-5,6,7,8-tetrahdyro[1,6]naphthyridine-3-yl)-N'-(3-bromophenyl)urea
N-(6-methyl-5,6,7,8-tetrahdyro[1,6]naphthyridine-3-yl)-N'-(4-trifluoromethylphenyl)urea
N-(6-methyl-5,6,7,8-tetrahydro[1,6]naphthyridine-3-yl)-N'-(phenyl)urea
N-(6-methyl-5,6,7,8-tetrahydro[1,6]naphthyridine-3-yl)-N'-(5-chloro-2,4-dimethoxyphenyl)urea or
N-(6-methyl-5,6,7,8-tetrahydro[1,6]naphthyridine-3-yl)-N'-(4-ethoxyphenyl)urea.

6. A process for the preparation of compounds of formula (I), which comprises reacting a compound of formula (II)



(II)

where R^{1A} is R^1 as defined for formula (I) or a group convertible to R^1, and
P is NH_2 or NCX, X being as defined for formula (I),

with a compound of formula (III)

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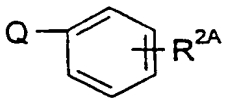

(III)

where Q is NCX or NH_2 and different from P, X being as defined for formula (I), and

R^{2A} is R^2 as defined for formula (I) or a group or groups convertible to R^2, and where required converting a R^{1A} or R^{2A} group to a R^1 or R^2 group, converting one R^1 or R^2 group to another R^1 or R^2 group, converting a salt product to the free base or another pharmaceutically acceptable salt, or converting a free base product to a pharmaceutically acceptable salt.

7. A pharmaceutical composition for use in the treatment and/or prophylaxis of anxiety, mania, depression, panic disorders and/or aggression, disorders associated with a subarachnoid haemorrhage or neural shock, the effects associated with withdrawal from substances of abuse such as cocaine, nicotine, alcohol and benzodiazepines, disorders treatable and/or preventable with anti-convulsive agents, such as epilepsy including post-traumatic epilepsy, Parkinson's disease, psychosis, migraine, cerebral ischaemia, Alzheimer's disease and other degenerative diseases such as Huntingdon's chorea, schizophrenia, obsessive compulsive disorders (OCD), neurological deficits associated with AIDS, sleep disorders (including circadian rhythm disorders, insomnia & narcolepsy), tics (e.g. Giles de la Tourette's syndrome), traumatic brain injury, tinnitus, neuralgia, especially trigeminal neuralgia, neuropathic pain, dental pain, cancer pain, inappropriate neuronal activity resulting in neurodysthesias in diseases such as diabetes, multiple sclerosis (MS) and motor neurone disease, ataxias, muscular rigidity (spasticity), temporomandibular joint dysfunction, and amyotrophic lateral sclerosis (ALS), which comprises a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier.

8. A method of treatment and/or prophylaxis of anxiety, mania, depression, panic disorders and/or aggression, disorders associated with a subarachnoid haemorrhage or neural shock, the effects associated with withdrawal from substances of abuse such as cocaine, nicotine, alcohol and benzodiazepines, disorders treatable and/or preventable with anti-convulsive agents, such as epilepsy including post-traumatic epilepsy, Parkinson's disease, psychosis, migraine, cerebral ischaemia, Alzheimer's disease and other degenerative diseases such as Huntingdon's chorea, schizophrenia, obsessive compulsive disorders (OCD), neurological deficits associated with AIDS, sleep disorders (including circadian rhythm disorders, insomnia & narcolepsy), tics (e.g. Giles de la Tourette's syndrome), traumatic brain injury, tinnitus, neuralgia, especially trigeminal neuralgia,

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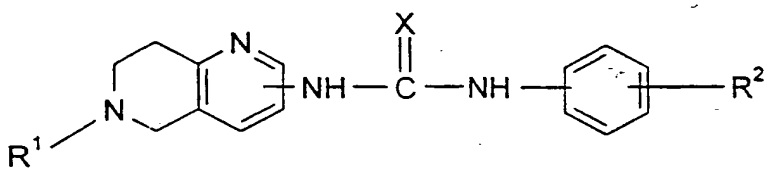
neuropathic pain, dental pain, cancer pain, inappropriate neuronal activity resulting in neurodysthesias in diseases such as diabetes, multiple sclerosis (MS) and motor neurone disease, ataxias, muscular rigidity (spasticity), temporomandibular joint dysfunction, and amyotrophic lateral sclerosis (ALS), comprising administering to the sufferer in need thereof an effective or prophylactic amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof.

9. Use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, for the manufacture of a medicament for the treatment and/or prophylaxis of anxiety, mania, depression, panic disorders and/or aggression, disorders associated with a subarachnoid haemorrhage or neural shock, the effects associated with withdrawal from substances of abuse such as cocaine, nicotine, alcohol and benzodiazepines, disorders treatable and/or preventable with anti-convulsive agents, such as epilepsy including post-traumatic epilepsy, Parkinson's disease, psychosis, migraine, cerebral ischaemia, Alzheimer's disease and other degenerative diseases such as Huntingdon's chorea, schizophrenia, obsessive compulsive disorders (OCD), neurological deficits associated with AIDS, sleep disorders (including circadian rhythm disorders, insomnia & narcolepsy), tics (e.g. Giles de la Tourette's syndrome), traumatic brain injury, tinnitus, neuralgia, especially trigeminal neuralgia, neuropathic pain, dental pain, cancer pain, inappropriate neuronal activity resulting in neurodysthesias in diseases such as diabetes, multiple sclerosis (MS) and motor neurone disease, ataxias, muscular rigidity (spasticity), temporomandibular joint dysfunction, and amyotrophic lateral sclerosis (ALS).

10. A compound of formula (I) or pharmaceutically acceptable salt thereof:



(I)

where R^1 is hydrogen, C_{1-6} alkyl, or phenylC_{1-6} alkyl.

R^2 is hydrogen or up to three substituents selected from halogen, CF_3, NO_2, CN, N_3, C_{1-6} alkylO-, C_{1-6} alkylS-, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkyl-C_{1-4}alkyl-, C_{1-6}alkenyl, C_{1-6}alkynyl, CF_3CO-, CF_3O C_{1-6}alkylCO-, C_{3-6}cycloalkylCO-, C_{3-6}cycloalkyl-C_{1-4}alkylCO-, phenyl, phenoxy, benzyloxy, benzoyl, phenyl-C_{1-4}alkyl-, heterocyclyl,

or $-NR^6R^7$ where R^6 is hydrogen or C_{1-4} alkyl, and R^7 is hydrogen, C_{1-4}alkyl, -CHO, $-CO_2C_{1-4}$alkyl or $-COC_{1-4}$alkyl.

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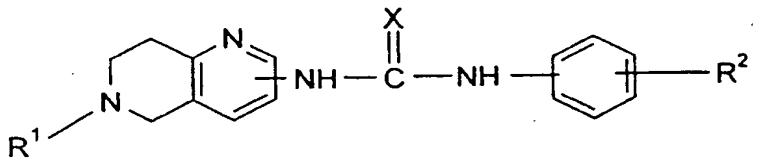

(I)

(57) Abstract

N–(naphthyridinyl)–N'–phenyl–ureas/thioureas of general formula (I) are useful for the treatment and/or prophylaxis of anxiety, mania, depression, panic disorders and/or aggression, disorders associated with a subarachnoid haemorrhage or neural shock, the effects associated with withdrawal from substances of abuse such as cocaine, nicotine, alcohol and benzodiazepines, disorders treatable and/or preventable with anti–convulsive agents, such as epilepsy including post–traumatic epilepsy, Parkinson's disease, psychosis, migraine, cerebral ischaemia, Alzheimer's disease and other degenerative diseases such as Huntingdon's chorea, schizophrenia, obsessive compulsive disorders (OCD), neurological deficits associated with AIDS, sleep disorders (including circadian rhythm disorders, insomnia and narcolepsy), tics (e.g. Giles de la Tourette's syndrome), traumatic brain injury, tinnitus, neuralgia, especially trigeminal neuralgia, neuropathic pain, dental pain, cancer pain, inappropriate neuronal activity resulting in neurodysthesias in diseases such as diabetes, multiple sclerosis (MS) and motor neurone disease, ataxias, muscular rigidity (spasticity), temporomandibular joint dysfunction, and amyotrophic lateral sclerosis (ALS).

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INTERNATIONAL SEARCH REPORT

ernational Application No
PCT/EP 98/05904

A. CLASSIFICATION OF SUBJECT MATTER
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According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
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Name and mailing address of the ISA	Authorized officer
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